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REVIEW ARTICLE

Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status*

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SUMMARY

The overlapping epidemiology of human immunodeficiency virus (HIV) infection and tuberculosis (TB) and the catastrophic consequences of the interactions between the two epidemics have led to increased morbidity and mortality due to HIV-associated TB. While effective therapy is available for both conditions, there are major challenges in the concurrent treatment of HIV and TB co-infection. This review examines the interactions between HIV and TB infections and reviews the current status of highly active antiretroviral therapy (HAART) in patients with co-infection. Specific questions relating to optimal timing of concurrent HAART, challenges to concurrent HAART, optimal regimens and future considerations are discussed.

KEY WORDS: TB; HIV; interactions; HAART

THE GLOBAL BURDEN of tuberculosis (TB) is enormous. In 2000, there were an estimated 8.3 million new cases of TB, 3.7 million of whom were smear-positive.[1] The vast majority of individuals with TB live in sub-Saharan Africa, the Western Pacific and South-East Asia,[1] where 34 million (85%) of the estimated 40 million people with human immunodeficiency virus (HIV) infection also live.[2] The overlapping epidemiology of HIV and TB infections has had catastrophic consequences. In 2000, 11% of all new TB cases in adults occurred in persons infected with HIV, and 9% of all new TB cases were directly attributable to HIV.[2] In addition, an estimated 12% of the 1.84 million deaths from TB were attributed to HIV infection and TB was the cause of 11% of all adult acquired immune-deficiency syndrome (AIDS) deaths.[2]

TUBERCULOSIS AND HIV INTERACTIONS

The interaction between HIV and TB infections is bidirectional. HIV infection increases the risk of both primary and reactivation TB,[3–5] and this risk increases markedly with advancing HIV disease.[5] At the time of TB diagnosis, most patients with co-infection have advanced HIV disease as defined by low CD4 cell counts and high viral loads or World Health Organization (WHO) Stage 3 and 4 disease.[5,6] This is not surprising, as the control of *Mycobacterium tuberculosis* infection is critically dependent on the presence of CD4+ T cells, CD8+ T cells and the production of cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α).[7,8] The development of active TB, on the other hand, is associated with increases in HIV viral load locally and systemically.[9,10] There is consequently an increased risk of progression to AIDS and death.[11–14]

RATIONALE FOR CONCURRENT ANTIRETROVIRAL THERAPY IN TB PATIENTS

The case fatality rates of HIV-associated TB are high; the estimated aggregate case fatality rate of HIV-infected TB is about 40%, and may be over 50% in many developing countries.[1,15] TB case fatality rates appear to be closely related to the prevalence of HIV infection, and HIV-related conditions may be the main cause for the increased death rate associated with HIV and TB co-infection.[2,15–18] While deaths in the first month of TB treatment may be due to TB, late deaths in co-infected persons are attributable to HIV disease progression.[15–18]

The current global TB control strategy using the WHO-recommended DOTS initiative alone is not sufficient to reduce TB morbidity and mortality in areas of high HIV prevalence.[19] While co-infected patients often receive quality TB treatment, the role of such treatment in slowing or reversing HIV disease progression is doubtful. In the early 1990s, Martin et al. showed that TB therapy had a positive influence on the CD4 lymphocyte count, with significant increases in CD4 cell counts.[20] However, recent studies have

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demonstrated no significant increases in CD4 cell counts or reduction in HIV-1 plasma loads during treatment of active TB in co-infected patients.[5,6,21] The failure of HIV plasma load to decrease in the initial months of anti-tuberculosis therapy has been associated with high systemic levels of TNF-α, which has been found to be sustained beyond the initial decline in mycobacterial load.[21] These data suggest that effective therapy to directly reduce HIV-1 plasma load in co-infected persons may be necessary during TB treatment.

The immunopathogenesis of HIV-associated TB[7–10] and modeling analyses[22] suggest that by inhibiting HIV viral replication and allowing for CD4+ T cell-related immune reconstitution, HAART will reduce both the incidence of TB and mortality. The use of HAART in TB-endemic areas has been associated with more than 80% reduction in the incidence of HIV-associated TB; the protective effect of HAART was seen at all stages of HIV disease, but was greatest in symptomatic patients and those with advanced disease.[23,24] Several observational studies have also found that the use of concurrent HAART in co-infected patients during TB treatment is associated with reduced mortality.[24–26] Taken together, these studies suggest that HAART has promise in reducing the high morbidity and mortality associated with TB-HIV co-infection.

WHEN SHOULD HAART BE STARTED?

Concomitant HAART during TB therapy is complicated by high pill burden, overlapping drug toxicities, concerns about drug-drug interactions and paradoxical immune reconstitution reactions.[27,28] These concerns have often been used to argue for delayed or deferred initiation of HAART during TB treatment.[27–29] In the clinical management of persons with active TB and HIV co-infection, there is consensus among experts that TB treatment should be started immediately following TB diagnosis,[28] but the timing of antiretroviral therapy from the time of starting TB treatment remains controversial. There are currently no published prospective controlled studies that have examined the optimal timing of HAART after initiation of TB therapy. Current treatment guidelines are based mainly on retrospective observational studies and expert opinion.[28,29] The American Thoracic Society, the Centers for Disease Control and Prevention (CDC) and the Infectious Diseases Society of America TB treatment guidelines suggest that delaying the initiation of antiretroviral therapy until 4–8 weeks after starting anti-tuberculosis therapy will allow for better evaluation of drug side effects, and reduce the severity of paradoxical reactions and adherence difficulties for the patient.[28] This recommendation is based largely on the high rates of treatment discontinuations due to adverse events observed in one study,[26] and experts' concerns about adherence when multiple medications are started at the same time. Lack of HAART in the patients with low CD4 cell counts is associated with increased risk of subsequent AIDS-defining illness and death.[26] We have also observed an increased risk of subsequent AIDS-defining illness in co-infected patients with CD4 cell counts $<100/\mu l$ in whom HAART was delayed.[30] Unlike the report by Dean et al.,[26] there were no discontinuations of TB or HIV therapy during concurrent therapy in our patients, probably because of the use of largely non-protease inhibitor-based regimens in those patients who initiated concurrent HAART.

The decision about when to initiate HAART in co-infected patients must balance the risk of HIV disease progression with the potential risk of drug toxicity. Although starting simultaneous concurrent therapy should be avoided in co-infected patients, there is a need for individualized assessment as to when to initiate HAART after starting TB therapy. A recent comparative study found that virologic, immunologic and clinical responses to HAART of HIV-1-infected TB patients treated concurrently with anti-tuberculosis therapy and HAART was similar to those of non-TB patients,[31] suggesting that we can not assume that concurrent HAART will be intolerable or lead to difficulties with adherence. As antiretroviral therapy become more compact and easy to manage, the risk of HIV disease progression must drive the decision about the timing of concurrent HAART in TB-HIV co-infected patients. Therefore, in patients with CD4 cell counts $<100/\mu l$ or advanced AIDS, initiation of concurrent HAART must be considered as early as possible. In patients with CD4 cell counts 100–200/μl, it is reasonable to defer HAART until 4–8 weeks after starting TB therapy to minimize potential adverse events associated with concurrent therapy. Unlike other opportunistic infections, TB is not necessarily a marker of advanced HIV disease, as TB can occur at any level of CD4 cell count. This implies that for individuals with CD4 cell count $>200/\mu l$ who otherwise have asymptomatic HIV disease, initiation of concurrent HAART should be based on symptoms of further AIDS-defining conditions, CD4 cell counts and rate of decline (if available), assessments of potential drug toxicities and drug-drug interactions, and readiness for initiation of HAART in accordance with current HIV treatment guidelines.[32,33]

CHALLENGES OF CONCURRENT HAART

The current standard of care for the treatment of HIV-1 infection is triple-drug therapy with two nucleoside or nucleotide reverse transcriptase inhibitor (NRTI/NtRTI) backbones in combination with a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI).[32,33] The multiple drug toxicities and the pharmacokinetic interactions between the

PIs and NNRTIs and the rifamycins, key components of combination therapy for HIV and TB disease, respectively, severely limit the options for optimal HAART regimens during rifamycin-based TB therapy.

Drug toxicities

Drug toxicity is a major challenge when multidrug therapy is required for any medical condition. Table 1 shows the antiretrovirals that are currently approved by the United States Food and Drug Administration (FDA) for the treatment of HIV-1 infection, and their potential toxicities. Although zalcitabine, delavirdine and ritonovir are approved for the treatment of HIV-1 infection, they are rarely used because of a high rate of toxicity, poor potency and drug-drug interactions, and are not listed in Table 1. Increased understanding and awareness of these toxicities by both clinicians and patients is important for their early recognition and management. Drug toxicity has been implicated as a major cause of discontinuation of antiretroviral therapy[34] and of interruptions of TB and/or HIV therapy during concurrent treatment of co-infection.[26]

Table 1 Approved antiretroviral drugs for the treatment of HIV-1 infection

Drug	Side effects	Monitoring or comment
Nucleoside/tide reverse transcriptase inhibitor (NRTI/NtRTI)	Class adverse reactions include lactic acidosis and steatosis	Regular clinical examination and determination of lactate levels as indicated
Abacavir (ABC)	Lactic acidosis with or without steatosis, nausea, vomiting, diarrhea and headache. Symptoms of hypersensitivity reactions include fever, skin rash, fatigue, malaise, gastrointestinal symptoms and respiratory symptoms	Hypersensitivity reactions can be fatal. Abacavir should be discontinued if hypersensitivity is suspected and should not be restarted
Didanosine (ddI)	Pancreatitis, peripheral neuropathy, gastrointestinal intolerance, hepatitis, lactic acidosis, rash and optic neuritis	Determination of amylase, lipase and lactate as clinically indicated
Emtricitabine (FTC)	Nausea, diarrhea, abnormal dreams, parasthesia, neuropathy and lactic acidosis and steatosis	Well tolerated
Lamivudine (3TC)	Nausea, diarrhea, abdominal pain, headache and insomnia. Lactic acidosis and steatosis and pancreatitis	Well tolerated. Determination of liver enzymes
Stavudine (d4T)	Lactic acidosis and steatosis, peripheral neuropathy, and lipoatrophy are attributed to mitochondrial toxicity. Gastrointestinal intolerance	Determination of liver enzymes
Tenofovir (TDF)	Gastrointestinal intolerance, headache, rare reports of renal insufficiency	Data are limited; well tolerated in clinical trials
Zidovudine (AZT)	Bone marrow suppression, myopathy, hepatitis, lactic acidosis and steatosis	Complete blood cell count with differential and creatine kinase as indicated
Non-nucleoside/tide reverse transcriptase inhibitor (NNRTI/NtRTI)	Class adverse reactions include skin rash and elevated liver enzymes	Regular clinical examination and measurement of liver enzyme levels
Efavirenz (EFV)	Rash, CNS side effects, hyperlipidemia, elevation of transaminases, false-positive cannabinoids test and teratogenicity	Should be avoided in pregnant women. Women with childbearing potential should be counseled about teratogenicity
Nevirapine (NVP)	Rash, Stevens-Johnson syndrome has been reported. Hepatotoxicity usually in the first 6–8 weeks	Increased risk of severe hepatotoxicity in women with CD4 count >250 cells/μl
Protease inhibitor (PI)	Class adverse effects include hyperglycemia, dyslipidemia and possibly bleeding in hemophilia	Regular clinical examination and measurement of liver enzymes, triglycerides and urine dipstick for glucose
Amprenavir	Gastrointestinal intolerance, nausea, vomiting, diarrhea, rash, headache, oral parasthesia transaminase elevation and hyperlipidemia	High pill burden
Atazanavir	Indirect hyperbilirubinemia, jaundice, gastrointestinal intolerance and P-R prolongation	Well tolerated and low pill burden
Fosamprenavir	Diarrhea, nausea, rash, vomiting, abdominal pain and headache	Use with caution in patients with sulfonamide allergy
Indinavir	Indirect hyperbilirubinemia, nephrolithiasis, alopecia and gastrointestinal intolerance, headache, thrombocytopenia and hemolytic anemia. Insulin resistance and hyperlidemia	
Lopinavir/ritonovir	Gastrointestinal intolerance, nausea, diarrhea, hyperlipidemia and insulin resistance	
Nefinavir	Gastrointestinal intolerance, nausea, diarrhea, abdominal pain, hyperlipidemia, insulin resistance	
Saquinavir	Gastrointestinal intolerance, nausea, diarrhea, abdominal pain, headache and transaminase elevation	
Fusion inhibitor		
Enfurtidine	Injection site reactions including induration, erythema, pain, nodules. Rarely bacterial pneumonia, systemic hypersensitivity and Guillian-Barre syndrome	An option for managing ARV treatment-experienced patients. Very expensive and can not be given orally

CNS = central nervous system; P-R = interval between the P and R waves in an electrocardiogram; ARV = antiretroviral

Table 2 Overlapping or additive toxicities due to antiretroviral drugs and first-line anti-tuberculosis agents

Toxicity	Antiretroviral agents	Anti-tuberculosis agents
Peripheral neuropathy	Stavudine, didanosine and zalcitabine	Isoniazid and ethambutol
Gastrointestinal intolerance	All	All
Hepatotoxicity	NVP, EFV, all NRTIs and PIs	Isoniazid, rifampin, RBT and pyrazinamide
Central nervous system toxicity	EFV	Isoniazid
Bone marrow suppression	AZT	RBT, rifampin
Skin rash	Abacavir, amprenavir, NVP, EFV and fosamprenavir	Isoniazid, rifampin and pyrazinamide
Ocular effects	Didanosine	Ethambutol and RBT

NVP = nevirapine; EFV = efavirenz; NRTIs = nucleoside reverse transcriptase inhibitors; PIs = protease inhibitors; RBT = rifabutin; AZT = zidovudine.

Concurrent therapy of TB-HIV co-infection requires concomitant administration of at least two to four different anti-tuberculosis agents and at least three antiretroviral drugs. The toxicities of some antiretrovirals may overlap with or can be additive to toxicities due to anti-tuberculosis medications (Table 2). Clinicians should be aware of these toxicities, and attempts should be made to use agents with minimal overlapping or additive toxicities. Patients need to be educated about drug toxicities and a monitoring plan outlined and discussed with them at start of therapy. Regularly scheduled clinical and laboratory monitoring in addition to patient education, and close communication between HIV care and TB clinicians, are critical to minimizing treatment discontinuation due to adverse events.

Drug-drug interactions between antiretroviral and anti-tuberculosis agents

The interactions between the rifamycins and the NNRTIs and the PIs are complex. The PIs and NNRTIs are metabolized mainly through the cytochrome P450 (CYP) 3A4 enzymes. The rifamycins induce the expression of CYP3A4 isoenzyme in the liver and intestines,[35,36] thereby greatly reducing the plasma concentration and exposure to the PIs and the NNRTIs when administered together.[27] In addition, rifampicin (RMP) increases the activity of the efflux multidrug transporter P-glycoprotein (P-gp), which contributes to the elimination of the PIs.[37,38] The reduction in plasma concentration of the PIs and NNRTIs during concurrent treatment with rifamycins can be associated with HIV treatment failure and emergence of drug resistance.

Rifamycins and NNRTIs

RMP reduces the area under the curve (AUC) of efavirenz (EFV) by 22–26%,[39,40] and nevirapine (NVP) by 31%.[41,42] The clinical significance of this reduction in exposure to the NNRTIs during concurrent RMP administration is unclear. However, there is controversy about the appropriate dose of these agents during concomitant RMP treatment, especially with EFV. While some experts suggest that the dose of EFV should be increased from 600 to 800 mg daily when co-administered with RMP,[40,43] others have found the 600 mg daily dose adequate.[44] The reduction in serum concentrations of NVP during concomitant RMP administration has not been associated with poor clinical or virological outcome in small studies.[41,42,45] This is thought to be due to the high therapeutic index of NVP. Until clinical and safety data are available for higher doses of NVP, the standard dose should be given with RMP.[41–43,45]

Rifabutin (RBT) is a less potent inducer of the CYP3A4 isoenzyme than RMP and it does not result in significant changes in serum EFV concentrations during concomitant administration, but it does reduce the serum concentration of NVP by 16%. Therefore, adjustment of the EFV or NVP dose during concurrent administration with RBT is not necessary.[33] However, unlike RMP, RBT is a substrate for the CYP3A4-isozyme and its serum concentration is reduced by 35% by the enzyme-inducing activity of EFV; however, the reduction by NVP is insignificant. Thus, the dose of RBT should be increased from 300 mg daily or three times a week to 450–600 mg daily or 600 mg three times a week when co-administered with EFV.[33,43]

The rifamycins and the PIs

The interaction between the rifamycins and the PIs is variable depending on the individual agents. RMP reduces the AUC of available PIs by 35–92%, and the reduction by RBT is in the range of 15–45%.[27,28,33,43] Of the available PIs, current pharmacokinetic data support the concomitant use of RMP and saquinavir[46] or lopinavir/ritonovir (kaletra®), boosted with an extra 300 mg of ritonovir,[47] but coadministration with other available PIs is contraindicated.[27,43] The pharmacokinetic interactions between RBT and the PIs are easier to manage than those with RMP, as RBT is a much less potent inducer of the CYP3A4 isoenzyme. This allows for more options in constructing concurrent PI-based HAART regimens during concurrent therapy with RBT-based TB therapy.[27,43] However, there are two major drawbacks. RBT and the PIs are expensive and are often not available in developing countries, the areas most affected by the HIV-TB co-epidemics. Secondly, adherence to both TB and HIV therapy is critical to achieve the expected drug levels using doses that are based on pharmacokinetic adjustments. Most PIs are inhibitors of the CYP3A4 isoenzyme and significantly reduce the clearance of RBT when co-administered, and thus a reduction of the RBT dose is required.[27,43]

Isoniazid and antiretroviral agents

Finally, the interactions between isoniazid (INH) and antiretroviral agents metabolized through the CYP3A4 may be clinically important, but have not been adequately studied. In vitro studies have shown that at clinically relevant concentrations INH reversibly inhibits the activity of CYP3A4 and CYP2C19 in human liver microsomes.[48,49] Co-administration of INH with the PIs and NNRTIs may result in significant drug interactions, especially when INH is given alone to treat latent TB infection in HIV co-infected patients receiving PI or NNRTI-based HAART. However, to our knowledge no pharmacokinetic or clinical studies have been conducted in humans.

WHAT CONCURRENT HAART REGIMENS?

For individuals with AIDS who are already receiving effective HAART at the time of TB diagnosis, HAART should be continued and appropriate anti-tuberculosis therapy initiated. For those who are not receiving HAART at the time of TB diagnosis, the selection of an appropriate HAART regimen will depend, among other factors, on the presence or absence of RMP in their anti-tuberculosis regimen.

HAART and RMP-based TB therapy

NNRTI-based regimens using a combination of two NRTI/NtRTIs with EFV or NVP can be administered concurrently with RMP-based TB therapy (Table 3A). Clinical experience with these regimens in TB patients is limited, and current recommendations are based on small pharmacokinetic studies.[39–42] The standard dose of NVP (200 mg twice daily) should be used during TB treatment with an RMP-containing regimen,[41–43] but the appropriate dose of EFV is controversial. EFV 600 mg[44] and 800 mg daily[50] have been used with regimens containing the standard dose of RMP, with excellent results. Although CDC guidelines suggest that the dose of EFV be increased to 800 mg daily when administered concurrently with RMP, safety data on EFV given 800 mg daily with or without RMP are limited.[43]

Co-administration of the available PIs with RMP is contraindicated, except for regimens containing saquinavir or lopinavir in dual combination with ritonovir.[33,43] Saquinavir/ritonovir 1000/100 mg or 400/400 mg twice daily and lopinavir/ritonovir 400/100 mg (kaletra®) boosted with 300 mg of ritonovir twice daily can be given during RMP-based TB treatment (Table 3A).[43] The toxicity of these combination regimens are not well studied, and concurrent therapy should be approached cautiously. Increased frequency of gastrointestinal intolerance and hepatotoxicity with the PI regimens containing ritonovir 400 mg twice daily may occur, and close monitoring of liver function test may be necessary.[43,47]

HAART and RBT-based regimens

Two NRTI/NtRTIs combined with any of the available PIs and NNRTIs can be given with RBT-based TB regimens, except for saquinavir, ritonovir or delavirdine (Table 3B).[27,28,43] The dose of nelfinavir and indinavir needs to be increased from 750 mg and 800 mg three times a day, respectively, to 1000 mg three times a day, to compensate for the effect of RBT on their metabolism. The dose of RBT also needs to be reduced, from 300 mg daily to 150 mg daily or 300 mg three times per week, when co-administered with indinavir, nelfinavir, amprenavir or fosamprenavir, and to 150 mg on alternate days or three times per week when coadministered with atazanavir, kaletra®, or ritonovir-boosted PI regimens (Table 3B). When RBT is given concurrently with EFV, the dose of RBT needs to be increased from 300 mg daily to 450–600 mg daily or 600 mg three times per week.[27,28,33,43,51]

HAART and non-rifamycin-based regimens

It is important to use RMP-containing regimens in persons with HIV-TB co-infection, as they have been associated with better responses to treatment,[52] improved survival,[53] and reduced recurrence rate of TB in HIV co-infected persons.[54] However, non-rifamycin TB therapy may be used in cases with known rifamycin resistance, or in areas where the rifamycins are not available or RMP is not used because directly observed therapy can not be provided. Standard HAART regimens, consisting of two NRTI/NtRTIs combined with any of the available PIs or NNRTIs generally recommended for persons with HIV infection,[32,33] can be given concurrently with a non-rifamycin TB regimen (Table 3C). In instances where an RMP-containing regimen is initially given during the induction phase of TB therapy and then switched to a non-rifamycin regimen to allow for either PI-based HAART to be initiated or self-administered therapy, RMP should be discontinued at least 2 weeks before the introduction of a PI-based regimen. This will allow for the induction effect of RMP on CYP3A4 to dissipate to avoid sub-therapeutic concentrations of the PI when initiated.

Nonucleoside/tide only regimens

The NRTI/NtRTIs have minimal interactions with rifamycins, except that RMP reduces the AUC of zidovudine (AZT) by 47% when co-administered.[55] The effect of RMP on intracellular AZT triphosphate, the active form of the drug, was not determined in the study, but the reduction in AZT plasma exposure is not expected to affect the antiviral activity and dosing of AZT.[55] Therefore, combination triple NRTI/NtRTIs regimens are attractive for concurrent application with RMP-based TB therapy. However, recent published data suggest that triple NRTI/NtRTI combinations may be less potent than NNRTI or PI-based regimens in the treatment of HIV infection, as they have

Table 3 Antiretroviral regimens and recommended doses that can be co-administered to treat HIV-1 infection in co-infected patients

A Rifampicin-based TB regimen

	Recommended dose	Nucleoside backbone*
NNRTI		
Efavirenz	600 or 800 mg/qd	2 NRTI/NtRTIs
Nevirapine	200 mg bid	2 NRTI/NtRTIs
PI		
Saquinavir/ritonovir	400/400 mg bid or 1000/100 mg bid	2 NRTI/NtRTIs
Lopinavir/ritonovir	400/400 mg bid†	2 NRTI/NtRTIs

B RBT-based TB regimen

	Recommended dose	Nucleoside backbone*	Recommended RBT dose
PI or NNRTI			
Indinavir	1000 mg tid	2 NRTI/NtRTIs	150 mg qd or 300 mg 3×/week
Nelfinavir	1000 mg tid	2 NRTI/NtRTIs	150 mg qd or 300 mg 3×/week
Amprenavir	1200 mg bid	2 NRTI/NtRTIs	150 mg qd or 300 mg 3×/week
Atazanavir	400 mg qd	2 NRTI/NtRTIs	150 mg qod or 150 mg 3×/week
Lopinavir/ritonovir	400/100 mg bid	2 NRTI/NtRTIs	150 mg qod or 150 mg 3×/week
Fosamprenavir	1400 mg bid	2 NRTI/NtRTIs	150 mg qd or 300 mg 3×/week
Ritonovir combined with atazanavir, amprenavir, indinavir, fosamprenavir, or saquinavir		2 NRTI/NtRTIs	150 mg qod or 150 mg 3×/week
Nevirapine	200 mg bid	2 NRTI/NtRTIs	300 mg qd or 300 mg 3×/week
Efavirenz	600 mg qd	2 NRTI/NtRTIs	600 mg qd or 600 mg qod

C Non-rifamycin-based TB regimen

	Usual dose	Nucleoside backbone*
PI		
Indinavir	800 mg tid	2 NRTI/NtRTIs
Nelfinavir	1250 mg bid or 750 mg tid	2 NRTI/NtRTIs
Amprenavir	1200 mg bid	2 NRTI/NtRTIs
Atazanavir	400 mg qd	2 NRTI/NtRTIs
Lopinavir/ritonovir	400/100 mg bid	2 NRTI/NtRTIs
Fosamprenavir	1400 mg bid	2 NRTI/NtRTIs
Saquinavir (soft gel capsule)	1200 mg tid	2 NRTI/NtRTIs
Ritonovir boosted PI		
Atazanavir/ritonovir	300/100 mg qd	2 NRTI/NtRTIs
Amprenavir/ritonovir	600/100 mg bid or 1200/200 mg qd	2 NRTI/NtRTIs
Indinavir/ritonovir	400/400 or 800/100 or 800/200 mg bid	2 NRTI/NtRTIs
Fosamprenavir/ritonovir	700/100 mg bid or 1400/200 mg qd	2 NRTI/NtRTIs
Saquinavir/ritonovir	400/400 mg or 1000/100 bid or 1600/200 qd	2 NRTI/NtRTIs
NNRTI		
Nevirapine	200 mg bid	2 NRTI/NtRTIs
Efavirenz	600 mg qd	2 NRTI/NtRTIs

* Combinations of stavudine + AZT, stavudine + zalcitabine, didanosine + zalcitabine and stavudine + didanosine should not be offered.
† Kaletra® 3 capsules plus ritonovir 300 mg bid; limited clinical data and tolerability in healthy volunteers was poor.
HIV = human immunodeficiency virus; TB = tuberculosis; NNRTI = non-nucleoside reverse transcriptase inhibitor; qd = once daily; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; bid = twice daily; RBT = rifabutin; PI = protease inhibitor; tid = three times a day; qod = every other day; AZT = zidovudine.

been associated with inferior virologic responses in clinical trials.[56–58] Thus, in line with current HIV guidelines,[32,33] NRTI/NtRTI-only regimens should generally not be considered as first-line regimens for the treatment of HIV-1 infection.

Concurrent HAART in resource-poor settings

In developing countries, the unavailability of RBT and the high cost of PIs, as well as the lack of treatment guidelines, severely limit the options and use of HAART during TB treatment. With the increasing availability of affordable generic antiretroviral agents, TB programs may be major points for identifying HIV-infected persons who require HAART. The preferred regimens for use in treatment naïve patients are EFV or NVP-based regimens,[29] which can be given concurrently with RMP-containing TB therapy. Alternatively, NNRTI or PI-based HAART regimens (when available) can be given with non-rifamycin-based TB therapy.

PARADOXICAL REACTIONS AND IMMUNE RESTORATION DISEASE

A sub-group of patients with HIV-TB co-infection will develop a paradoxical exacerbation of TB symptoms or signs after initiation of TB treatment, or more commonly after initiation of concurrent antiretroviral therapy.[59,60] This phenomenon is referred to as immune restoration disease (IRD), and is characterized by transient worsening or appearance of new symptoms, signs, or radiographic manifestations of tuberculosis. These paradoxical responses to treatment of TB-HIV co-infection are thought to be due to enhancement of anti-tuberculosis inflammatory responses in infected tissues as a result of restoration immune reactivity to *M. tuberculosis* antigens. The pathogenesis of paradoxical responses is believed to be related to restoration of pathogen-specific immune reactivity against pre-existing pathogens leading to inflammatory reactions in infected tissues.[60]

The true frequency of paradoxical reactions in TB patients receiving concurrent HAART is unknown; reports are as high as 35–36% in some studies,[59,60] while another study reported only 7%.[61] Among a cohort of 144 co-infected patients treated with NVP-based HAART in India, 11 developed IRD; the incidence of IRD in that cohort was calculated as 15.2 cases per 100 patient years.[62] Risk factors that have been associated with paradoxical reactions in observational studies include initiation of concurrent HAART, low CD4 cell counts, extra-pulmonary site of disease and greater reductions in viral loads as a result of HAART.[57,58] The temporal association of paradoxical reactions with initiation of HAART has led some authors to suggest that concurrent HAART should be delayed to reduce the frequency of IRD in patients receiving TB therapy.[27,59,60] Kumarasamy et al. found no association between development of IRD and duration of TB treatment before initiation of HAART.[62] It is important to note that the clinical impact of paradoxical reactions on TB or HIV disease outcome is not clear, but no long-term sequelae have been observed.[60] Thus, these reactions should be recognized as inflammatory responses to successful therapy; continuation of TB and HIV therapy may result in sustained protective immunity and clearance of the TB infection. The management of paradoxical reactions should include an evaluation to exclude treatment failure and concurrent opportunistic infections. Treatment of TB disease to reduce the antigenic burden should be continued and effective HAART can be continued in most cases. The suspected immune basis of the syndrome suggests that therapy with anti-inflammatory agents or steroids may be helpful. If severe or life-threatening symptoms due to IRD occur, steroids should be given and HAART may be temporarily withheld.

ROLE OF DIRECTLY OBSERVED THERAPY

Directly observed therapy (DOT) has been credited with improved TB outcomes and with preventing the emergence of drug resistance in observational studies.[63,64] However, the superiority of DOT over self-administered therapy (SAT) for the treatment of TB in developing countries is yet to be proven. Well controlled, randomized trials performed in South Africa[65] and Pakistan[66] showed similar treatment completion and cure rates for DOT and SAT TB treatment, while investigators in Thailand found higher treatment completion and cure rates in patients assigned to DOT compared to SAT.[67] The success of DOT programs has been attributed to significant financial input, which resulted in improved overall program quality, such as patient/supervisor interactions; supervision of dosing in isolation of program improvement may be less relevant.[68] One difficulty in studying the true impact of DOT is that in most instances DOT never exists outside of the DOTS program or context; DOT is one of the five tenets of DOTS strategy which builds a program of support and evaluation for the patient. The critical issue is that adherence is addressed and ensured; it is likely that there are several mechanisms to do this in the context of a well functioning infrastructure for care delivery.

The concept of DOT to deliver HAART may be reasonable in some settings, despite the major differences between TB and HIV therapy. While the duration of TB treatment is 6–12 months, and doses can be given twice or thrice weekly, HIV therapy requires lifetime therapy, and current recommended dosing is once to thrice daily.[69] In addition, TB has a long generation time and slow emergence of resistance, while HIV has a short generation time and error-prone replication with rapid emergence of resistance. Despite these differences, the apparent success of TB DOT programs[63,64] has led some authors to propose that modified DOT be adapted to deliver HAART to selected HIV-infected patients.[70] Published data on the utility and efficacy of combined HAART and TB DOT in treating co-infection are non-existent. While the concept of combined HAART and TB DOT holds some promise and has been proposed as a model for delivery of HAART to co-infected patients in resource-poor countries,[71] rigorous assessment of its utility is needed. It may be reasonable to use modified DOT to deliver TB and HIV medications during the induction phase of TB treatment, especially in settings where communication facilities are poor; DOT workers may also monitor adverse events as HAART is introduced. Studies of these proposed programs are needed. The current lack of data to characterize the benefits of DOT HAART has led some authors to advocate restraint in the enthusiasm for DOT to deliver HAART as part of routine HIV care in resource-poor settings.[72]

FUTURE CONSIDERATIONS

Major progress has been made in understanding the interactions between HIV and TB infections. There have also been fundamental insights into the components of concurrent HAART during TB therapy, yet critical clinical management questions remain unanswered. The timing of HAART after starting TB therapy and the optimum concurrent HAART regimens are unknown and require urgent evaluation in controlled studies. In addition, management issues that require careful evaluation include the frequency and management of paradoxical reactions, the role of adjunctive therapy with non-steroidal anti-inflammatory agents or steroids in reducing the frequency of paradoxical reactions, monitoring concurrent HAART in resource-poor settings—outcomes with or without laboratory support, and the role of modified DOT compared to SAT for delivering combined HAART and TB treatment. Clinical studies to evaluate the implications of the pharmacokinetic interactions between the rifamycins and the NNRTIs and PIs are necessary to determine the appropriate dosing of the NNRTIs when coadministered with RMP. The concept of mixed induction and inhibition of CYP3A4 isoenzyme by RMP and ritonovir or INH on the metabolism of PIs and NNRTIs during treatment of co-infection has important clinical implications and should be studied. Scaling up concurrent HAART programs will require urgent, increased financial commitment and research capabilities in the areas most affected by the co-epidemics of HIV and TB. Observational, hypothesis-driven operational research programs should be integral components of TB and HIV programs as such initiatives are implemented in both industrialized and resource-poor countries. Timely review of treatment guidelines is necessary as relevant data become available.

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RÉSUMÉ

Le chevauchement de l'épidémie de l'infection par le virus de l'immunodéficience humaine (VIH) et par la tuberculose (TB) et les conséquences catastrophiques des interactions entre ces deux épidémies ont entraîné un accroissement de la morbidité et de la mortalité dues à la TB associée au VIH. Alors qu'une thérapeutique efficiente est disponible pour chacune des deux affections, le traitement parallèle de la co-infection VIH et TB comporte des défis majeurs. Cette revue examine les interactions entre les infections VIH et TB et fait la revue de la situation actuelle concernant la thérapie antirétrovirale hautement active (HAART) chez les patients co-infectés. Nous y discutons des questions spécifiques en relation avec la chronologie optimale du HAART concomitant, les défis concernant le HAART concomitant, les régimes optimaux ainsi que des considérations d'avenir.

RESUMEN

La epidemiología concurrente de la infección por el virus de la inmunodeficiencia humana (VIH) y la tuberculosis (TB) y las consecuencias catastróficas de las interacciones entre ambas epidemias han generado un incremento en la morbilidad y la mortalidad de la TB asociada con el VIH. Si bien existe un tratamiento eficaz para cada enfermedad, el tratamiento simultáneo de la coinfección TB y VIH plantea desafíos importantes. La presente revisión analiza las interacciones entre la infección por el VIH y la TB y revisa el estado actual del tratamiento antirretrovírico altamente activo (HAART) en pacientes con coinfección. Se discuten aspectos específicos relacionados con el tiempo óptimo para el HAART simultáneo, los desafíos del HAART simultáneo, los esquemas óptimos y otras consideraciones para el futuro.